REMARKS

Claims 1-34 are pending in this application. Claims 10-33 have been withdrawn from consideration by the Examiner in view of the restriction and election requirements, which have been made final, but have not been canceled due to potential rejoinder. Claims 1, 3-5 and 34 have been amended. The amended claims do not include new matter, as indicated below.

Claims 1 and 34 have been amended to clarify that a respective promiscuous hybridizes, rather than is capable of hybridizing, to a target sequence that is shared between at least two of the target polynucleotides. These claims have also been amended to clarify that a predefined combination of probes hybridizes, rather than is capable of hybridizing, to the at least two target sequences of a respective target polynucleotide. These amendments merely delete redundant language and are clearly supported by the original language of claims 1 and 34.

Claims 1 and 34 have also been amended to recite that the number of probes in the claimed set of oligonucleotide probes is less than the number of target polynucleotides in the plurality of target polynucleotides that are the subject of detection. This amendment finds support in the specification as originally filed at least in paragraphs **[0036]**, **[0037]**, **[0082]**, **[0084]** and **[0087]**.

Claim 3 has been amended to clarify that at least one non-promiscuous probe hybridizes, rather than is capable of hybridizing, to a unique target sequence of a single target polynucleotide.

Claim 4 has been amended to clarify that at least one probe hybridizes, rather than is capable of hybridizing, to a pivot sequence.

Claim 5 has been amended to clarify that at least one degenerate oligonucleotide probe hybridizes, rather than is capable of hybridizing, to a redundant target sequence.

For the foregoing reasons, Applicants respectfully assert that the amendments made herein are fully supported by the specification and do not include new matter.

Rejection of Claims under 35 U.S.C. § 102

Hogan *et al.* (U.S. Patent No. 5,541,308)

The Examiner rejects claims 1-4, 6 and 34 under 35 U.S.C. § 102(b) as being allegedly anticipated by Hogan *et al.* As a basis for this rejection, the Examiner opines that the phrases "respective promiscuous probe," "predefined combination" and "specificity of detection" are relative phrases which are interpreted broadly to encompass *any* probe relationship, *any* combination and *any* degree of specificity because the claims have not provided guidance for defining the claimed "respective," "predefined" and "specificity". Applicants respectfully disagree with Examiner's position because the meaning of these phrases can be readily determined from the language of the claims themselves and especially when read in the light of the written description of the invention in the application.

The phrase "respective promiscuous probe" is used in the claims to mean an individual promiscuous probe belonging to the set of promiscuous probes recited in the preamble of claims 1 and 34. This is a normal usage of "respective" and is consistent with the definition in The American Heritage Dictionary of the English Language (Fourth Edition. Copyright 2000 Houghton Mifflin Company), *i.e.*, "Relating to two or more persons or things regarded individually…"

The phrase "predefined combination" is defined in the definitions in paragraph **[0068]** of the subject application as follows:

> The term "predefined combination" refers to a combination of oligonucleotide probes that are at least substantially complementary to, or would be expected to hybridise with, target sequences of a single target polynucleotide. Target sequences which are recognised by a predefined combination of probes encompass known target sequences or a potential or hypothetical combination of at least one known target sequence and at least one redundant target sequence as defined herein. Such potential combination of target sequences can be recognised by oligonucleotide probes belonging to a predefined assemblage as described hereinafter.

Therefore, the combination of probes is said to be "predefined" because before an assay is performed with the claimed set of oligonucleotides, individual combinations of promiscuous probes would need to be defined so that each combination would be expected to hybridize with

target sequences in a single target polynucleotide of the plurality of different target polynucleotides to be assayed.

The phrase "specificity of detection" is used in the subject application to mean detection of a target polynucleotide so that it may be correctly assigned to a category that is distinguished from other categories, where a category can comprise a single polynucleotide or group of related polynucleotides (e.g., a gene family, genotype, species or higher taxon or grouping of related species).

When read in the context of the phrase "said predefined combination providing specificity of detection of said at least one target polynucleotide," in claim 1 and the phrase "each providing specificity of detection of a different target polynucleotide" in clam 2, it follows that the phrase "providing specificity of detection" means a finite and fixed capability, namely providing specific detection of a particular target polynucleotide, rather than a relative capability that could mean any degree of specificity. A person of ordinary skill in the biotechnology art clearly would understand and know that the phrase "providing specificity" is commonly used in this way in molecular biology and is consistent with the definition of "specificity" in *The American Heritage Dictionary of the English Language* (Fourth Edition. Copyright 2000 Houghton Mifflin Company), *i.e.* "1. Explicitly set forth; definite. 2. Relating to, characterizing, or distinguishing a species. 3. Special, distinctive, or unique…"

The above construction of the phrase "specificity of detection" is clearly supported by various passages in the instant specification. For example, paragraph **[0001]** of the description states:

> More particularly, the present invention relates to a set of oligonucleotide probes, wherein two or more probes, in combination, can specifically detect a target polynucleotide and wherein different combinations of probes provide specificity for detecting and distinguishing different target polynucleotides.

Additionally, paragraph **[0083]** states:

> Despite the promiscuity of a respective promiscuous probe hybridising to more than one target polynucleotide, a particular target polynucleotide can be specifically detected by detecting hybridisation thereto of at least two promiscuous probes, wherein different target polynucleotides are identified by different combinations of such probes.

Accordingly, in contradistinction to the Examiner's allegations, the cited phrases have a clear meaning that would be readily apparent to a person of skill in the art from the language of the claims themselves, and especially when read in the light of the description of the invention in the application.

From the bottom of page 3 to the middle of page 5 of the Office Action, the Examiner alleges that Hogan *et al.* disclose a set of probes for detecting at least one target polynucleotide (e.g. *Mycobacterium avium)* from a plurality of different targets (Column 12, line 58-Column 13, line 35). Specifically, in her rejection of claims 1 and 34, the Examiner asserts that this reference teaches a set of probes that comprises a collection of different promiscuous probes (*i.e.* genus-specific probes 1-4, Example 8, lines 15-53) wherein the probes are capable of hybridizing to sequences shared by at least two target sequences (*i.e.* Mycobacterium genus) wherein a predefined combination of promiscuous probes hybridizes to at least two targets and provides specificity of detection (Tables 22-23). Applicants respectfully disagree.

Hogan *et al.* do not disclose a set of probes at column 12, line 58, to column 13, line 35. A single specific probe is disclosed in column 12 at lines 54 and 55.

Hogan *et al.* disclose a set of probes in Example 8 (columns 27-29) but the statements in this example indicate that the *Mycobacterium* genus is the sole target of those probes.

Additionally, columns 12 and 13 and columns 27-29 do not indicate that *Mycobacterium avium* is distinguished from other possible species using promiscuous probes. *Mycobacterium avium*, the species identified at column 12, is not identified as a target in columns 27 to 29, where the probes disclosed by Hogan *et al.* are discussed. Additionally, *Mycobacterium avium* is not distinguished (specifically detected) from the other *Mycobacterium* species in Example 8 (columns 27 to 29).

Many species from the *Mycobacterium* genus are listed in Table 22 (column 28), but the different species do not represent individual targets or target polynucleotides in Example 8

within the meaning of the instant claims. Further, Hogan *et al.* make no statements that indicate different species are individual targets. As the probes are not species-specific, the different species are not distinguished or identified (that is, they are not specifically detected) using the probes defined in this example (column 27).

Columns 27-29 do not indicate that the probes are capable of hybridizing to sequences shared by at least two targets, as they identify only one target, namely the *Mycobacterium* genus.

In accordance with how "target polynucleotide" is defined in the instant claims, this means that the *Mycobacterium* rRNA genes that are the subject of detection in Hogan *et al.* either constitute different target polynucleotides or a single target group of related polynucleotides. Assuming the former construction, the probes disclosed by Hogan *et al.* do not meet every element recited in claims 1 and 34. This is because Hogan *et al.* do not explicitly or implicitly disclose a specific *Mycobacterium* rRNA gene that comprises at least <u>two</u> target sequences shared with <u>one or more other</u> *Mycobacterium* rRNA genes, and wherein a predefined combination of promiscuous probes hybridizes to the at least two target sequences of the specific *Mycobacterium* rRNA gene, to thereby provide specificity of detection of that gene. By contrast, Hogan *et al.* discloses a set of probes that detects all members of the genus *Mycobacterium* rather than detecting specific members of that genus. This conclusion is clearly supported in Hogan *et al.* at several passages, including the passage at column 27, lines 22 to 24, which states:

> "...we have designed probes which detect all members of the genus Mycobacterium without cross reacting to the related genera.";

and the passage at column 27, lines 39 and 40, which reads:

> "The following sequences were characterized and shown to be specific for the genus Mycobacterium.";

as well as the passage at column 28 lines 9 to 14, which states:

> "The results are shown in Table 22 and indicate that the probes hybridize to organisms in the genus *Mycobacterium* and that a combination of probes will detect <u>all members of the genus</u>. Table 23 shows that the probes do not react with other closely related bacteria." [emphasis added].

Accordingly, if the *Mycobacterium* rRNA genes disclosed in Hogan *et al.* were construed as being different target polynucleotides, then Hogan *et al.* do not define a combination of probes

that hybridize to at least two targets, as (i) they do not define two targets, and (ii) they do not define any combination of probes that provides specificity of detection for a single *Mycobacterium* rRNA gene.

In addition, although a combination of probes is mentioned at column 28, line 11, Hogan *et al.* do not define the combination of probes, nor do they disclose if the combination is defined before the probes are used, as would have to be the case if it was a "predefined combination."

Further, Hogan *et al.* do not disclose the present inventors' strategy for using promiscuous probes in different combinations to decrease the number of oligonucleotide probes required for detecting and distinguishing between a plurality of different target polynucleotides. Accordingly, Hogan *et al.* do not teach a set of probes in which the number of probes of the set is less than the number of target polynucleotides that are the subject of detection by the set.

Assuming the alternate construction of "target polynucleotide" were adopted to mean that the *Mycobacterium* rRNA genes constitute a single target group of related polynucleotides, then the probes taught by Hogan *et al.* also do not meet every element in claims 1 and 34. This is because the set of probes recited in claims 1 and 34 requires at least one of the target polynucleotides to comprise at least two target sequences shared with <u>one or more other</u> target polynucleotides. This would mean that the probes of Hogan *et al.*, would need to hybridize with genes (e.g., rRNA genes) that are not members of the genus *Mycobacterium*. However, Hogan *et al.* only teaches a set of probes that detects all members of the genus *Mycobacterium* and that does not cross react with related genera (see the passage at column 27, lines 17 to 24). Accordingly, Hogan *et al.* do not implicitly or explicitly teach 'promiscuous probes' that meet all the recitations of the claims.

Consequently, Hogan *et al.* fail to disclose each and every one of the elements defined in claims 1 and 34.

Turning now to the rejection of claim 2, the Examiner asserts that Hogan *et al.* disclose a set of probes further comprising a plurality of different predefined combination of probes, each providing specificity of detection (*i.e.* genus-specific probes 1-4, Example 8, lines 15-53 and species-specific probes for *(M. avium*, *M. intracellulare* and *M. tuberculosis)* (Column 13, lines 2-35 and Tables 1-23). The Examiner apparently has misread this claim as requiring different predefined combinations of probes, rather than different predefined combinations of *promiscuous* probes. As

demonstrated above, Hogan *et al.* do not teach any specific target polynucleotide (e.g., a specific *Mycobacterium* rRNA gene) that comprises at least <u>two</u> target sequences shared with <u>one or more other</u> target polynucleotide (e.g., one or more other *Mycobacterium* rRNA genes), wherein a predefined combination of promiscuous probes hybridizes to the at least two target sequences of the specific target polynucleotide, to thereby provide specificity of detection of that polynucleotide. Accordingly, Hogan *et al.* could not possible teach *other* predefined combination of promiscuous probes when they disclose *none*. Additionally, Hogan *et al.* do not disclose any combinations of *promiscuous* probes that provide specificity of detection of a single target polynucleotide.

The Examiner also rejects claim 3, allegedly because Hogan *et al.* disclose at least one probe capable of hybridizing to a unique target (*i.e. M. Avium, M. intracellulare, and M. tuberculosis)* (Column 13, lines 2-35 and Tables 1-23). Although Applicants concede that Hogan *et al.* teach unique target sequences, they do not teach a predefined combination of promiscuous probes that hybridizes to at least two target sequences of a specific target polynucleotide and that provides specificity of detection of that target polynucleotide. Hogan *et al.* merely disclose a single combination of probes (Table 22) that hybridizes to only one target polynucleotide, namely the *Mycobacterium* genus of rRNA genes.

The Examiner also rejects claim 4, alleging that Hogan *et al.* disclose at least one probe "capable" of hybridizing to a pivot sequence. The Examiner opines that genus-specific probes as illustrated in Table 22 of Hogan *et al.* are "capable" of hybridizing to a pivot sequence as defined in paragraph **[0066]** of the specification. In support of this position, the Examiner asserts that the recitation "capable of hybridizing to" is a recitation of intended use which does not define or describe the structure or composition of the probe and that this recitation has thus been interpreted broadly to encompass possible hybridization between any nucleotides of the probe and target. Applicants have amended the language of claim 4 to recite at least one probe that *hybridizes* to a pivot sequence, thereby mooting this rejection.

Further, Applicants submit that Hogan *et al.* do not disclose a pivot sequence in Example 8. Instead, they disclose sequences that are found in (specific for) all members of the genus, as indicated for example at column 27, line 22, and column 27, line 39. In addition, there is no

material in Example 8, including Table 22, which indicates that the target sequences of probes 1 to 4 are pivot sequences.

The Examiner rejects claim 6, alleging that Hogan *et al.* disclose probes that are immobilized on a solid support (*i.e.* magnetic bead Example 8, Column 28, lines 2-14). Although Applicants admit that Hogan *et al.* teach immobilization of probes after hybridization with target polynucleotides, the cited reference does not teach a predefined combination of promiscuous probes that hybridizes to at least two target sequences of a specific target polynucleotide and that provides specificity of detection of that target polynucleotide. Consequently, this reference does not teach each and every one of the elements recited in claim 6.

From the foregoing, Applicants conclude that Hogan *et al.* do not teach (1) the detection of individual members of a plurality of different polynucleotides, (2) a target polynucleotide that comprises at least two target sequences shared between one or more other target polynucleotides, (3) a predefined combination of promiscuous probes, (3) the use of a predefined combination of promiscuous probes to provide specificity of detection of a single target polynucleotide, (4) a set of probes in which the number of probes is less than the number of target polynucleotides that are the subject of detection, and (5) a pivot sequence that divides two or more polynucleotides into distinct groups. Consequently, Hogan *et al.* fail to disclose each and every one of the essential elements defined in the pending claims. For these reasons, Applicants respectfully urge the Examiner to reconsider and withdraw the rejection of claims 1-4, 6 and 34 pursuant to 35 U.S.C. § 102(b).

Gentalen *et al.* (U.S. Patent No. 6,306,643)

The Examiner rejects claims 1-4, 6-9 and 34 under 35 U.S.C. § 102(e) as being allegedly anticipated by Gentalen *et al.* The Examiner alleges that Gentalen *et al.* disclose a set of probes for detecting at least one target polynucleotide, the set comprising a collection of different promiscuous probes capable of hybridizing to a target shared between two target polynucleotides (common probe and polymorphic site) wherein a predetermined combination of probes is capable of hybridizing to at least two target sequences providing specificity of detection "(Column 2, line 51-Column , line 31; Column 8, line 45-Column 10, line 8 and claim 8)" [*sic*]. Applicants respectfully traverse this ground of rejection.

The present invention is based on a novel strategy for *decreasing* the number of oligonucleotide probes required for detecting and distinguishing between a plurality of target polynucleotides. The strategy involves using a set of oligonucleotide probes to detect different target polynucleotides, wherein the set includes a collection of promiscuous probes, wherein each promiscuous probe is capable of hybridizing to a predetermined sub-sequence or target sequence shared between at least two target polynucleotides and wherein the target polynucleotides to be detected comprise two or more target sequences shared with one or more other target polynucleotides. Despite the promiscuity of a respective promiscuous probe hybridizing to more than one target polynucleotide, a particular target polynucleotide can be specifically detected by detecting hybridization thereto of at least two promiscuous probes, wherein different target polynucleotides are identified by different combinations of such probes. See for example, paragraphs **[0082]** and **[0083]** of the instant specification. The use of such combinations of probes permits the design of fewer probes to detect a finite number of target polynucleotides than would otherwise be required if target-specific probes were used. See for example, paragraphs **[0036]**, **[0037]**, **[0082]**, **[0084]** and **[0087]**. Accordingly, independent claims 1 and 34 have been amended to recite that the number of probes in the claimed set of oligonucleotide probes is less than the number of target polynucleotides that are the subject of detection.

In contrast, Gentalen *et al.* do not disclose this feature that the number of probes in the claimed set of oligonucleotide probes is less than the number of target polynucleotides that are the subject of detection. In fact, Gentalen *et al.* disclose probe arrays that require two different probes to hybridize to different segments of the same target molecule in a cooperative manner. This cooperative binding is employed to distinguish between a single target polynucleotide containing two segments of interest (*i.e.*, two different polymorphic sites), and two target molecules, each containing one of the segments of interest (*i.e.*, one of the polymorphic sites) (see column 8, lines 46-65). Therefore, at most, Gentalen *et al.* disclose the use of two probes for detecting a first allele of a polymorphic gene, a third probe for detecting a second allele of a polymorphic gene and a fourth probe for detecting a third allele of a polymorphic gene. Accordingly, Gentalen *et al.* teach the use of more probes (*i.e.*, 4) than the number of alleles to be detected (*i.e.*, 3) rather than less probes than the number of target polynucleotides to be

detected, as required by the pending claims. As such claims 1 and 34 are novel over Gentalen *et al.*

Since claims 2-4 and 6-9 also recite that the number of probes of the set is less than the number of target polynucleotides that are the subject of detection by the set, by virtue of their dependence on claim 1, then these claims must also be novel over Gentalen *et al.*

Consequently, Gentalen *et al.* fail to teach each and every one of the essential elements defined in the pending claims and the Examiner is respectfully urged, therefore, to reconsider and withdraw the rejection of claims 1-4, 6-9 and 34 pursuant to 35 U.S.C. § 102(e).

Rejection of Claims under 35 U.S.C. § 103

The Examiner rejects claim 5 under 35 U.S.C. § 103(a) as being unpatentable over Gentalen *et al.* in view of Lockhart *et al.* (U.S. Pat. No. 6,329,140). Specifically, the Examiner makes the same allegations as those mentioned above in respect of Gentalen *et al.* but concedes that this reference does not specifically teach a probe set comprising a degenerate probe. The Examiner asserts, however, that Lockhart *et al.* teach a similar probe set comprising a degenerate probe wherein the degenerate probe is useful for analyzing polynucleotides encoding polypeptide sequences of interest (column 2, lines 22-44). On this basis, the Examiner opines that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the probe sets of Gentalen *et al.* by including degenerate probes for the asserted expected benefit of analyzing clinically important polynucleotides and the encoding polypeptide sequences of interest as taught by Lockhart *et al.* (Column 2, lines 22-44). Applicants respectfully traverse this ground of rejection.

Gentalen *et al.* do not disclose the claimed probe set for the reasons set forth above and thus, even when combined with the teachings of Lockhart *et al.*, fail to teach or reasonably suggest each and every one of the elements recited in claim 5. Besides, a skilled person would not be motivated to modify the probe set of Gentalen *et al.* to include a degenerate probe as taught by Lockhart *et al.* because Gentalen *et al.* is primarily concerned with the detection of nucleotide polymorphisms, which are sequence specific and which do not relate or constitute conserved target sequences.

The Examiner rejects claims 5 and 7-9 under 35 U.S.C. § 103(a) as being unpatentable over Hogan *et al.* in view of Lockhart *et al.* (U.S. Pat. No. 6,329,140). The Examiner makes the same allegations as those mentioned above in respect of Hogan *et al.* but admits that they do not specifically teach a probe set comprising a degenerate probe, a high-density array of probes or a linkage via a spacer. It is asserted, however, that Lockhart *et al.* teach these missing elements at column 2, lines 22-44, column 28, lines 2-14, and column 12, lines 1-5, and that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the probe sets of Hogan *et al.* by including a degenerate probe, a high-density array of probes or a linkage *via* a spacer as taught by Lockhart *et al.*

As explained above, however, Hogan *et al.* do not disclose the claimed set of probes and thus, even when combined with the teachings of Lockhart *et al.*, fail to teach or reasonably suggest each and every one of the elements recited in claim 5 and 7-9. Moreover, a person of skill in the art would not be motivated to modify the probe set of Hogan *et al.* to include a degenerate probe as taught by Lockhart *et al.* because the probe set taught by Hogan *et al.* already contains generate probes that hybridize to target sequences conserved between different *Mycobacterium* rRNA genes. At best, the combination of Hogan *et al.* and Lockhart *et al.* would motivate a skilled person to use a *Mycobacterium* rRNA genus-specific probe in a high-density array or to link it *via* a spacer to a support.

For the foregoing reasons, Applicants respectfully urge the Examiner to reconsider and withdraw the rejection of claims 5 and 9 pursuant to 35 USC § 103(a).

Rejection of Claims under 35 U.S.C. § 101 (Double Patenting)

Claims 1-9 are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as claims 1-9 of copending Application No. 10/343,170. Applicants propose to cancel claims 1-9 of that copending application upon an indication from the Examiner that the pending claims are otherwise be in condition for allowance.

Reconsideration and withdrawal of all rejections, rejoinder of withdrawn claims and an early Notice of all pending claims are respectfully solicited.

Respectfully submitted,

MARK JOHN GIBBS *et al.*

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(Date)

ALAN S. NADEL
Registration No. 27,363
AKIN GUMP STRAUSS HAUER & FELD LLP
One Commerce Square
2005 Market Street, Suite 2200
Philadelphia, PA 19103-7013
Telephone: 215-965-1200
Direct Dial: 215-965-1280
Facsimile: 215-965-1210
E-Mail: anadel@akingump.com

ASN/hg